REMARKS

Status of the claims

Claims 1-10 and 12-27 were pending. By amendment herein, claims 16 to 27 have been canceled, without prejudice or disclaimer. In addition, claims 6 and 7 have been amended for proper antecedent basis. Thus, claims 1-10 and 12-15 are pending as shown above.

Rejections Withdrawn

Applicants note with appreciation withdrawal of the previous rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103. (Office Action, pages 2-3).

35 U.S.C. § 112, 1st paragraph, new matter

Claims 16-27, newly added in the previous response, were rejected under 35 U.S.C. § 112, 1st paragraph as alleged not complying with the written description requirement for containing new matter, particularly a negative proviso excluding liposomal formulations wherein when L is –X– (C=O)–Y, Y is not NH when X is O. (Office Action, pages 3-4).

Cancellation of claims 16-27 without prejudice or disclaimer obviate the foregoing rejection.

35 U.S.C. § 112, 2nd paragraph

Claims 16-27 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for reciting "L is –X– (C=O)–Y–." (Office Action, pages 4-5). In addition, claims 6, 7, and 19 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for improper antecedent basis of the recitation "wherein said preparing." *Id.*

Applicants thank the Examiner for her careful attention to the claim language. Claims 16-27 have been canceled and claims 6 and 7 have been amended to remove the recitation "wherein said preparing." Thus, the rejections have been obviated.

35 U.S.C. § 102(b)

Claims 16-22 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 01/05873 (hereinafter "Zalipsky"). (Office Action, page 6). It was alleged that Zalipsky teaches that same formulations as set forth in the claims and that these formulations would "inherently" reduce liposome-induced complement activation upon in vivo administration. *Id.*

Claims 16-22 have been canceled, thus the rejection may be withdrawn.

35 U.S.C. § 103(a)

Claims 1-10, 12, 13 and 16-25 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Zalipsky in view of U.S. Patent No. 5,786,387 (hereinafter "Watanabe") and in further view of Szebeni et al. (2002) *J. Liposome Research* 12:165-172 (hereinafter "Szebeni"). (Office Action, pages 7-10). Zalipsky was for disclosing liposomes containing PEG-substituted neutral polymers and for "inherently" teaching reduction in complement activation. *Id.* Watanabe was cited for teaching a lipid double chain derivative containing a polyoxyethylene that can be incorporated into a liposome and used to carry anticancer drugs and Szebeni was cited for teaching negatively charged liposome (i.e. Doxil™) were potent complement activators as compared to neutral liposomes which caused no complement activation. *Id.*

In addition, claims 14, 15, 26 and 27 were rejected as allegedly obvious over Zalipsky in view of Watanabe, in further view of Szebeni and in further view of U.S. Patent No. 5,945,122 (hereinafter "Abra"). (Office Action, page 11). Zalipsky, Watanabe and Szebeni were cited as above and Abra was cited for teaching a liposome composition with an entrapped cisplatin. *Id.*

The pending claims are directed to methods of reducing liposome-induced complement-activation to particular liposome structures that entrap therapeutics. None of the cited references teach such methods. As acknowledged, Zalipsky does not teach or using neutral liposomes to encapsulate chemotherapeutic agents, while Watanabe and Szebeni fail to teach the particularly claimed neutral liposomal structures, let alone

neutral liposomes with entrapped chemotherpeutics. Thus, the references do not teach all of the elements of the claims.

Indeed, Szebeni does not teach anything about the structure of their neutral liposomes other than noting only that they lack "2K-PEG-DSPE or HSPG." See, page 167 of Szebeni. Nor does Szebeni teach anything about how the neutral liposomes of unspecified structure actually function *in vivo* regarding complement activation. Rather, Szebeni provides a single sentence stating that neutral liposomes (of unspecified structure) do not induce complement activation *in vitro*. Given the clear teachings of the specification that (1) neutral liposomal preparations can induce complement activation and (2) *in vitro* complement activation does not necessarily correspond to *in vivo* complement activation, the skilled artisan would have no reasonable expectation that that modifying Szebeni's neutral liposome into one of the particularly claimed structures and entrapping a chemotherapeutic in such a liposome would reduce complement activation in vivo. See, e.g., preparation 7 of Table 5; paragraph [0054] noting that two neutral liposome preparations gave vastly different responses in vitro as compared to in vivo and stating "results suggest that not all neutral lipopolymers are capable of reducing the induction of complement activation caused upon *in vivo* administration of a liposome preparation." In light of the fact that the skilled artisan would not have had any reasonable expectation from Szebeni that neutral liposomes as claimed would reduce complement activation, the rejection should be withdrawn.

In addition, the obviousness rejection is also improper because of secondary considerations of non-obviousness. The Supreme Court recently reaffirmed, in *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. ___, 127 S. Ct. 1727 (2007), that secondary considerations such as long-felt need and unexpected results must be considered in determining obviousness. See, also, Patent Office "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007," emphasis added):

> Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved need, failure of others, and unexpected results.

As noted above, the evidence of record establishes that the claimed methods solve a long-felt need and provide unexpected results. There was a long-felt need to reduce complement activation *in vivo* associated with certain liposomal compositions and this need was not solved by the cited references. See, e.g., paragraphs [0004] to [0006] of the specification. Furthermore, it was unexpected that the particular neutral liposomes claimed would reduce complement activation, given that the skilled artisan would have known that charge is not necessarily a determining factor in whether a liposomal preparation induces complement activation. See, also, paragraph [0007] noting other factors and that the role of these factors has not been clarified.

Thus, the particularly claimed methods resulted in unexpected reduction in complement activation and solved a long-felt need. For at least these reasons, withdrawal of the rejection is in order.

CONCLUSION

In light of the amendments and remarks presented in this paper, it is believed that the claims are in condition for allowance.

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Respectfully submitted,

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